



(19)

Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11)

**EP 1 088 564 A1**

(12)

**EUROPEAN PATENT APPLICATION**

(43) Date of publication:  
04.04.2001 Bulletin 2001/14

(51) Int Cl.7: **A61L 33/10**, A61L 33/06,  
A61L 27/34, A61L 31/10

(21) Application number: **99203203.7**

(22) Date of filing: **30.09.1999**

(84) Designated Contracting States:  
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU  
MC NL PT SE**  
Designated Extension States:  
**AL LT LV MK RO SI**

(72) Inventors:  
• **van Beusekom, Heleen**  
3000 RD Rotterdam (NL)  
• **van der Giessen, Wim**  
3015 GD Rotterdam (NL)

(71) Applicant: **Orbus Medical Technologies, Inc.**  
Ft Lauderdale, Florida 33309 (US)

(74) Representative: **Visser-LuIrink, Gesina, Dr.**  
Octrooibureau Lioc,  
P.O. Box 13363  
3507 LJ Utrecht (NL)

(54) **Intraluminal device, coating for such device, as well as a method for preparing the intraluminal device**

(57) Disclosed is an intraluminal device, suitable for implantation in a body. Said intraluminal device is provided with a coating which comprises:

50-97% heparan sulfate;  
1-20% laminin;  
0,2-15% type IV collagen.

Furthermore a coating is disclosed, which coating is suitable for the above mentioned device, as well as a method for preparing such device, comprising the steps of:

- providing a intraluminal device for implantation in a body;
- preparing a composition, comprising, in about 50 mg/ml solvent:

50-97% heparan sulfate;  
1-20% laminin;  
0,2-15% type IV collagen;

the solvent being a suitable buffer or water;

- dipping the intraluminal device in the composition; and
- drying the dipped intraluminal device.

**EP 1 088 564 A1**

## Description

[0001] The present invention relates to an intraluminal device, suitable for implantation in a body, which intraluminal device is provided with a coating.

[0002] Intraluminal devices of the above mentioned type are generally known and applied. Such devices are for example applied in the treatment of blood vessel blockage in which the blocked blood vessel first is dilated, followed by placing a vascular prosthesis, in particular a stent, in the blood vessel in order to keep the vessel in the dilated state. This treatment does, however, give rise to several problems with regard to the vascular healing, as the natural healing process after such an operation is not regulated and as a consequence thereof undesirable local thrombosis can take place.

[0003] After the above implantation, the intraluminal device interacts with the vesselwall surface and the bloodstream. The endothelialization of the intraluminal device is generally complete within two to three months after implantation. During this period the patient is at risk of thrombotic occlusion.

[0004] There are several techniques available for controlling the thrombogenicity of intraluminal devices, such as for example vascular stents. Thrombosis can passively be prevented by creating an inert surface which improves the surface characteristics that influence thrombosis. Such characteristics comprise, for example, charge, wettability and topography.

[0005] Thrombosis can also be prevented by binding one or more active components which inhibit thrombosis to the stent surface in order to actively prevent thrombosis. Examples of such components are prostaglandins, heparins, other thrombin inhibitors, or enzymes such as ADPase.

[0006] Furthermore, thrombosis can be controlled by mimicking at the stent surface an already completed thrombotic response. This can be achieved coating the stent surface with fibrin, thereby creating a controlled thrombus in vitro, as polymerized and stabilised fibrin is no longer thrombogenic.

[0007] Thrombus formation can also be limited by disguising the stent surface with plasma proteins such as albumin, gamma globulins or phospholipids, which causes the skipping of certain phases in the proteinaceous - thrombotic - response.

[0008] The above mentioned coatings have an anti-proliferative effect; the growth velocity is inhibited in order to prevent thrombosis or restenosis.

[0009] The present invention aims to provide for an intraluminal device according to the preamble which after implantation in a body adds to an improvement of the process of vascular healing and which provides for an improved anti-thrombogenicity.

[0010] In order to achieve this the present invention is directed to an intraluminal device according to the preamble, which is characterised in that the coating comprises:

50-97% heparan sulfate;  
1-20% laminin;  
0,2-15% type IV collagen.

[0011] By providing an intraluminal device with a coating of the above specified composition a suitable substrate is provided on which endothelial cells can grow. During the growth the endothelial cells create their own matrix upon which to grow and remain attached. Given that the normal endothelium is non-thrombogenic, providing a coating suitable for endothelial cell growth can shorten the period during which a patient is at risk of thrombotic occlusion.

[0012] All of the above components are also naturally present in the basement membrane of the blood vessel wall and are suitable for endothelial cell growth. The heparan sulfate is an important component as it has an effective anti-thrombogenic effect. Laminin can contribute to the binding properties of the coating to, for example DNA and RNA in gene therapy. Finally, type IV collagen adds to an improved attachment of the coating on the intraluminal device as well as a better attachment of the endothelial cells on the coated surface of the intraluminal device.

[0013] The coating according to the present invention provides a surface which is higher up in the natural healing cycle. The coating provides a fertile rich environment for endothelial cells and regulated thrombus formation. Thus, contrary to the coatings according to the prior art, the coating according to the present invention has a proliferative effect. As a result of proliferative effect, the vascular wound healing is stimulated thereby decreasing the period during which thrombosis can occur.

[0014] In a particular embodiment the coating comprises:

75-95% heparan sulfate;  
3-10% laminin;  
0,5-10% type IV collagen.

[0015] In a further preferred embodiment the coating comprises entactin and nidogen.

[0016] Said compounds add to the structural integrity of the coating and also improve the attachment of the endothelial - cells to the intraluminal device coating.

[0017] In another advantageous embodiment the coating furthermore comprises a growth factor.

[0018] Growth factors in general stimulate the growth of - for example, endothelial - cells and therefore enhance the proliferative effect.

[0019] Preferably, the growth factor is chosen from the group consisting of bFGF, IGF, TGF- $\beta_1$  and VEGF-145.

[0020] The different growth factors bFGF (basic fibroblast growth factor), IGF (insulin like growth factor), TGF- $\beta_1$  (transforming growth factor), and VEGF-145 (vascular endothelial growth factor) all add to the growth of specific components.

[0021] In order to prevent any risk of infection, the coating advantageously comprises an antibiotic.

[0022] In order to have an optimal effect the antibiotic should be a broad spectrum antibiotic, such as gentamycine.

[0023] In a preferred embodiment the coating of the intraluminal device according to the present invention comprises vitronectin.

[0024] Vitronectin offers a good basis for cell attachment; moreover it binds Reopro® which is a compound with a known anti-thrombotic effect. By incorporating vitronectin in the intraluminal device coating and administering Reopro® to a patient, thrombosis is even further prevented.

[0025] In a particular preferred embodiment of the intraluminal device according to the present invention, the coating comprises:

85-95% heparan sulfate;  
5-6% laminin;  
3-4% type IV collagen;  
0,5-1,5% entactin and nidogen;  
0,001-1% growth factors;  
0,001-1% antibiotic.

[0026] In a preferred embodiment the intraluminal device comprises a vascular prosthesis such as a stent or a graft. The stent as well as the graft can be prepared from different materials known to the person skilled in the art.

[0027] The coated intraluminal device according to the present invention can furthermore be used as a basis for therapies such as, for example, drug delivery and gene therapy. Drugs can be binded to the coating such that the release thereof is controlled. As mentioned in the above, the presence of laminin in the coating improves the bindings which are desired and required in gene therapy. It is also possible to provide for one or more radioactive molecules in the coating in order to inhibit cell growth, if desired.

[0028] The present invention also relates to a coating suitable for application to a intraluminal device according to the present invention.

[0029] It will be clear that such coating may also be used on other substrates which can be implanted in a body.

[0030] The present invention also relates to a method for preparing a intraluminal device according to the above, comprising the steps of:

- providing a intraluminal device for implantation in a body;
- preparing a composition, comprising, in about 50 mg/ml solvent:

50-97% heparan sulfate;  
1-20% laminin;  
0,2-15% type IV collagen;

the solvent being a suitable buffer or water;

- dipping the intraluminal device in the composition; and
- drying the dipped intraluminal device.

[0031] The method as such is very simple and easy to perform and moreover is not time-consuming. The drying step can take place with or without heated or forced air drying.

[0032] Preferred embodiments of the method according to the present invention are given in claims 13-17.

## Claims

1. Intraluminal device, suitable for implantation in a body, which device is provided with a coating, characterised in that the coating comprises:

50-97% heparan sulfate;  
1-20% laminin;  
0,2-15% type IV collagen.

2. Intraluminal device according to claim 1, characterised in that the coating comprises:

75-95% heparan sulfate;  
3-10% laminin;  
0,5-10% type IV collagen.

3. Intraluminal device according to claim 1 or 2, characterised in that the coating comprises entactin and nidogen.

4. Intraluminal device according to claim 1-3, characterised in that the coating furthermore comprises a growth factor.

5. Intraluminal device according to claim 4, characterised in that the growth factor is chosen from the group consisting of bFGF, IGF, TGF- $\beta$  and VEGF-145.

6. Intraluminal device according one or more of the preceding claims, characterised in that the coating comprises an antibiotic.

7. Intraluminal device according to claim 6, characterised in that the antibiotic comprises gentamycine.

8. Intraluminal device according to one or more of the preceding claims, characterised in that the coating comprises vitronectine.

9. Intraluminal device according to one or more of the preceding claims, characterised in that the coating comprises:

85-95% heparan sulfate;  
 5-6% laminin;;  
 3-4% type IV collagen;  
 0,5-1,5% entactin and nidogen;  
 0,001-1% growth factors;  
 0,001-1% antibiotic.

5

10. Intraluminal device according to one or more of the preceding claims, characterised in that the prosthesis comprises a stent or a graft. 10
11. Coating suitable for a intraluminal device according to one or more of the preceding claims 1-10.
12. Method for preparing a intraluminal device according to one or more of the claims 1-10, comprising the steps of: 15
  - providing a intraluminal device for implantation in a body; 20
  - preparing a composition, comprising, in about 50 mg/ml solvent:
    - 50-97% heparan sulfate;
    - 1-20% laminin; 25
    - 0,2-15% type IV collagen;
    - the solvent being a suitable buffer or water;
  - dipping the intraluminal device in the composition; and 30
  - drying the dipped intraluminal device.
13. Method according to claim 12, characterised in that the composition comprises entactin and nidogen. 35
14. Method according to claim 12 or 13, characterised in that the composition furthermore comprises a growth factor, chosen from the group consisting of bFGF, IGF, TGF- $\beta$  and VEGF-145. 40
15. Method according to one or more of claims 12-14, characterised in that the the composition comprises an antibiotic.
16. Method according to one or more of claims 12-15, characterised in that the composition comprises vitronectine. 45
17. Method according to one or more of the claims 12-16, characterised in that the composition comprises: 50

85-95% heparan sulfate;  
 5-6% laminin;;  
 3-4% type IV collagen;  
 0,5-1,5% entactin and nidogen;  
 0,001-1% growth factors;  
 0,001-1% antibiotic.

55



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number  
EP 99 20 3203

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	SCHNEIDER A ET AL: "An improved method for endothelial cell seeding on polytetrafluoroethylene small caliber vascular grafts." JOURNAL OF VASCULAR SURGERY, (1992 APR) 15 (4) 649-56. , XP000884442 * the whole document *	1,2	A61L33/10 A61L33/06 A61L27/34 A61L31/10
A	EP 0 945 145 A (SHIMIZU YASUHIKO ;TAPIC INTERNATIONAL CO LTD (JP)) 29 September 1999 (1999-09-29) * claims; example 1 *	1-17	
A	WO 95 31944 A (VEC TEC INC) 30 November 1995 (1995-11-30) * claims; examples *	1-17	
A	WO 99 01167 A (MINNESOTA MINING & MFG) 14 January 1999 (1999-01-14) * page 3, line 1 - line 5 *	1-17	
A	US 4 963 146 A (LI SHU-TUNG) 16 October 1990 (1990-10-16) * claims *	1-17	TECHNICAL FIELDS SEARCHED (Int.Cl.7) A61L
A	DATABASE WPI Section Ch, Week 198630 Derwent Publications Ltd., London, GB; Class D16, AN 1986-194636 XP002131679 & JP 61 128974 A (ADV KAIHATSU KENKYU), 17 June 1986 (1986-06-17) * abstract *	1,2	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 1 March 2000	Examiner ESPINOSA, M
CATEGORY OF CITED DOCUMENTS X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document		T: theory or principle underlying the invention E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons &: member of the same patent family, corresponding document	

EPO FORM 1503 (03.02) (P/0001)

**ANNEX TO THE EUROPEAN SEARCH REPORT  
ON EUROPEAN PATENT APPLICATION NO.**

EP 99 20 3203

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

01-03-2000

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0945145	A	29-09-1999	WO	9822155 A	28-05-1998
WO 9531944	A	30-11-1995	US	5643712 A	01-07-1997
			AU	2517395 A	18-12-1995
			AU	2595195 A	18-12-1995
			EP	0759692 A	05-03-1997
			WO	9531897 A	30-11-1995
			US	5699793 A	23-12-1997
WO 9901167	A	14-01-1999	AU	5166298 A	25-01-1999
US 4963146	A	16-10-1990	US	5026381 A	25-06-1991
JP 61128974	A	17-06-1986	NONE		

EPO FORM 1069

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82